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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,783	01/16/2004	Yuk-Ming Dennis Lo	016285-003710US	8146

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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,783	LO ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *12-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/30/04, 4/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I and the hGRH gene in the reply filed on June 26, 2006 is acknowledged. The traversal is on the ground(s) that the inventions are closely related and thereby a search for invention I would overlap with a search of the remaining inventions. This is not found persuasive because a search for the subject matter of invention I is not in fact co-extensive with a search of inventions II-VIII. For instance, a search for methods for detecting hCRH mRNA levels as a means for diagnosing pre-eclampsia would not provide one with all of the references applicable to kits containing primers for amplifying hCRH mRNA and control mRNA in the amount of that of an average pregnant woman, methods for detecting trisomy, kits for comprising reagents for detecting chromosomally normal and abnormal fetuses, methods for detecting trisomy 21, methods for detecting the distinct disorder of pre-term labor, kits comprising primers and control mRNAs representative of the amount of mRNA present in a woman who delivers at term, methods which diagnose the distinct condition of pregnancy, and kits containing primers and control mRNA representative of the amount of mRNA in the blood of an average non-pregnant woman. While a search of, e. g, invention I, may identify a reference that is also identified by a search of invention II, III, IV, V, VI, VII, VIII, or IX, such a fact does not indicate that a complete search of each of inventions I-IX is co-extensive with one another. Further, as discussed in the previous Office action, a finding that the method of invention I is novel and unobvious over the prior art does not necessarily extend to a finding that the kits and methods of inventions

II-IX are also novel and unobvious over the prior art. Similarly, a finding that the method of invention I is anticipated or obvious over the prior art does not necessarily extend to a finding that the kits and methods of inventions II-IX are also anticipated or obvious over the prior art. Thereby, it is maintained that inventions I-IX are patentably distinct and that undue burden would be required to examine each of these inventions together with the elected invention of Group I.

The response further traverses the restriction requirement by asserting that the MPEP 803.04 states that ten sequences normally constitute a reasonable number of sequences for search for examination purposes and thereby it would not require an undue search burden to search each of the genes set forth in the claims. This argument has been fully considered but is not persuasive. With respect to claims to nucleic acids, the MPEP states that the requirements of 37 CFR 1.141 have been partially waived to "permit a reasonable number of such nucleotide sequences to be claimed in a single application." The MPEP further states that "**normally** ten sequences constitute a reasonable number for examination purposes and that "**up to 10** independent and distinct nucleotide sequences" (emphasis added) may be examined in a single application. Thereby, the MPEP does not in fact state that 10 nucleotide sequences will be examined in each application. In the present situation, it is maintained that undue burden would be required to search and examine each of the recited patentably distinct genes. Each of the nucleic acids consist of a distinct nucleotide sequence and encode for proteins having distinct functional properties, and thereby the nucleic acids differ in their structure and effect. A search for methods of diagnosing preeclampsia by detecting

hCRH would not be co-extensive with a search for methods for diagnosing preeclampsia by detecting hCG-beta, hPL, KISS1, TPF12, PLAC1 and GAPDH.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

2. Claims 1-11 are objected to because the claim includes subject matter of the non-elected inventions, namely the non-elected mRNAs of hCG-beta, hPL, KISS1, TPF12, PLAC1 and GAPDH.

Specification

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-25 because a paper copy of a sequence listing and a computer readable copy of the sequence listing have not been filed. As the sequence disclosures in this application are not pertinent to the claimed invention and in the interest of compact prosecution, this case has been examined on the merits. However, in response to this Office action, Applicants must comply with the requirements of 37 CFR 1.821-1.825. In particular, Applicant is required to submit a CRF and paper copy of the Sequence Listing containing each of the sequences recited in the specification (see, for example, pages 17, 20 and 21), an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final step of the claims. The claims are drawn to methods for diagnosing, monitoring or predicting preeclampsia. However, the claims recite a final step in which an increase or decrease in mRNA indicates preeclampsia or risk of developing preeclampsia. However, the claims do not recite any active steps which accomplish the objective of monitoring preeclampsia. Thereby, it is unclear as to whether the claims are intended to include methods of monitoring preeclampisa, in addition to methods for diagnosing or predicting the risk of preeclampsia or whether the claims are intended to be limited only to methods for diagnosing or predicting the risk of preeclampsia. In the former case, the claims omit the essential process steps required to permit the monitoring of preeclampsia

Claims 1-11 are also indefinite over the recitation of "an increase or a decrease in the amount of mRNA from the standard control" because it is unclear as to whether this phrase refers to the mRNA present in the standard control or refers to a comparison between the mRNA of the standard control and a test mRNA from the pregnant woman.

The claims are further indefinite because it is unclear as to how both an increase and a decrease in hCRH mRNA is indicative of preeclampsia or risk of preeclampsia.

Claims 5 and 6 are indefinite over the recitation of "woman is during the first trimester" and "women is during the second or third trimester" because it is not clear as to what is meant by these phrases. The claims should be amended to clarify that the blood is from a woman in her first or second or third trimester of gestation.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for diagnosing or predicting the risk of preeclampsia in a pregnant women comprising (i) quantitatively determining the amount of extracellular hCRH mRNA in the serum or plasma of a woman in the third trimester of gestation, and (ii) comparing the amount of mRNA from step (i) to a standard control representing the amount of hCRH mRNA in a serum or plasma sample of an average non-preeclamptic pregnant woman, wherein if there is an increase in the amount of mRNA from the pregnant woman as compared to the standard control, it is determined that the pregnant woman has preeclampsia or is at risk of developing preeclampsia, does not reasonably provide enablement for methods for diagnosing, monitoring or predicting preeclampsia comprising quantitatively determining the amount of cellular or extracellular hCRH mRNA in a blood sample from a pregnant woman in any trimester of pregnancy, and comparing the amount of hCRH mRNA in said blood sample to that of a

standard control wherein either an increase or a decrease in the quantity of hCRH mRNA in the blood sample from the pregnant woman indicates preeclampsia or risk of developing preeclampsia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for diagnosing, monitoring or predicting preeclampsia comprising quantitatively determining the amount of hCRH mRNA in a pregnant woman's blood, and comparing the amount of said hCRH mRNA with that of a standard control, wherein either an increase or a decrease in the amount of said hCRH in the pregnant woman's blood indicates preeclampsia or a risk of developing preeclampsia.

The claims encompass the analysis of both cellular and extracellular hCRH mRNA levels.

The claims also encompass the analysis of hCRH mRNA levels in any trimester of pregnancy.

Further, the claims encompass detecting either an increase or a decrease in hCRH mRNA levels as indicative of preeclampsia or risk of developing preeclampsia.

Nature of the Invention:

The claims encompass methods of diagnosing preeclampsia by analyzing hCRH mRNA present in blood, serum or plasma. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the results of a study of hCRH mRNA levels in the plasma of pregnant woman in the third trimester of gestation (page 16). It was determined that hCRH mRNA plasma levels were significantly increased in pregnant woman in the third trimester of gestation having preeclampsia as compared to a control group of pregnant woman not having preeclampsia (page 19). Additionally, the specification teaches that hCRH mRNA is cleared from the maternal plasma within 2 hours of delivery. In particular, while hCRH mRNA was detected in 4 pre-delivery pregnant woman, hCRH mRNA was not detected in any post-delivery woman (page 18).

The Predictability or Unpredictability of the Art and Degree of Experimentation:

It is highly unpredictable as to whether the results obtained in plasma samples can be extrapolated to cellular blood samples. The specification teaches that hCRH mRNA is detectable in both preeclamptic and non-preeclamptic pregnant woman.

However, there are no teachings in the specification regarding a change in the level of cellular hCRH mRNAs in preeclamptic woman versus non-preeclamptic woman. The specification does not provide sufficient information regarding the mechanism by which the presence of acellular or cellular hCRH mRNA levels contribute to the occurrence of preeclampsia. However, it is known that hCRH is synthesized in the placenta and is released into the maternal circulation. As indicated in the post-filing date art of Ng (Clinical Chemistry. 2003. 45: 727-731; cited in the IDS), hCRH mRNA is derived from the fetus and it is believed that hCRH mRNA is released by the placenta into the maternal plasma. While fetal derived cells are detectable in maternal blood, there is no showing in the present specification that fetal cells expressing hCRH mRNAs are specifically detectable in maternal blood and that that there are higher levels of hCRH mRNAs in fetal cells of preeclampsia woman than in non-preeclampsia woman. Thereby, it is unpredictable as to whether extracellular hCRH mRNA plasma levels correlate with cellular hCRH mRNA levels. Accordingly, it is further unpredictable as to whether the results obtained with hCRH mRNA levels in plasma samples can be extrapolated to cellular blood samples.

Additionally, it is highly unpredictable as to whether the occurrence of or risk of developing preeclampsia can be diagnosed in woman in the first or second trimester of pregnancy by assaying for hCRH mRNA levels. The specification does not provide sufficient information regarding levels of hCRH mRNA in blood or plasma/serum samples of preeclamptic versus non-preeclamptic pregnant woman in the first or second trimester of pregnancy. In particular, there is no information available to support a

conclusion that the cellular or acellular levels of hCRH mRNA are higher in early stages of pregnancy in preeclamptic woman versus controls. Since preeclampsia generally occurs in later stages of pregnancy, it would be expected that higher CRH mRNA levels would also only occur at later stages of pregnancy. In the absence of a clear understanding between hCRH plasma levels and the occurrence of preeclampsia, it is unpredictable as to whether the results obtained in woman in the third trimester of pregnancy can be extrapolated to woman in the first or second trimester of pregnancy.

Amount of Direction or Guidance Provided by the Specification:

Establishing a correlation between the cellular or extracellular occurrence of nucleic acids and a disease is highly unpredictable and can only be established by trial and error experimentation. A number of highly variable factors influence whether a RNA is present in a biological sample and whether the presence of the RNA is indicative of disease. For instance, as discussed in the specification, apoptotic events may be responsible for the release of hCRH mRNA into the plasma or serum in preeclamptic woman. However, there is no showing in the specification of a corresponding overall increase in hCRH mRNA cellular levels in blood.

The specification does not provide any specific guidance as to how to overcome the known factors which effect the ability to reproducibly detect particular mRNAs in blood as indicative of a condition. There are no teachings in the specification to establish that one can apply the disclosed method of analyzing plasma samples for hCRH mRNA to other types of blood samples, and particularly cellular blood samples. The specification also does not provide sufficient guidance as to how to extend the

findings obtained with woman in the third trimester of pregnancy to woman in the first or second trimester of pregnancy.

Further, no specific guidance is provided in the specification as to how to apply the claimed method to one in which the detection of a decrease in hCRH mRNA levels is used to determine an increased risk of having or developing preeclampsia. All data presented in the specification indicate that only an increase in the level of hCRH plasma/serum mRNA is associated with preeclampsia.

Working Examples:

The specification does not specifically exemplify any methods in which preeclampsia is diagnosed in woman in the first or second trimester of pregnancy or in which preeclampsia is diagnosed by assaying for hCRH mRNA levels in a cellular blood sample.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genetech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of

one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification does not teach a representative number of stages of pregnancy at which preeclampsia can be diagnosed and does not teach a representative number of cellular blood samples which can be analyzed for hCRH mRNA levels to diagnose preeclampsia. In view of the high level of unpredictability in the art and the lack of guidance provided by the specification and prior art, undue experimentation would be required to practice the claimed invention.

Priority

6. Regarding claim 4, provisional application 60/440,906 does not provide support for the concept of detecting the hCRH mRNA by mass spectrometry. Accordingly, claim 4 is entitled only to the present filing date of January 16, 2004.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ng (Clinical Chemistry. 2003: 727-731; cited in the IDS) in view of Monforte (U.S. Patent NO. 6,635,452).

Ng et al disclose a method for diagnosing preeclampsia comprising (i) quantitatively determining the amount of extracellular hCRH mRNA in the plasma of a pregnant woman, and (ii) comparing the amount of mRNA from step (i) to a standard control representing the amount of hCRH mRNA in a plasma sample of an average non-preeclamptic pregnant woman, wherein if there is an increase in the amount of mRNA from the pregnant woman as compared to the standard control, it is determined that the pregnant woman has preeclampsia or is at risk of developing preeclampsia (see pages 728 and 730). Ng teaches that the quantity of hCRH mRNA is determined by real-time quantitative RT-PCR. Ng does not teach determining the quantity of hCRH mRNA using mass spectrometry.

However, Monforte teaches methods for determining the quantity of mRNA present in a sample wherein said methods comprise performing mass spectrometry (paragraph 29).

In view of the teachings of Monforte, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ng so as to have detected the hCRH mRNA by mass spectrometry in place of real-

time RT-PCR in order to have provided an equally effective and rapid means for determining the quantity of hCRH mRNA in maternal blood samples.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
July 12, 2006

CARLA J. MYERS
PRIMARY EXAMINER

Notice to Comply	Application No. 10/759,783	Applicant(s) Lo et al	
	Examiner Carla Myers	Art Unit 1634	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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